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EXAMINER	
KAUFMAN, C	
ART UNIT	PAPER NUMBER
1646	21

DATE MAILED: 03/09/99

Below is a communication from the EXAMINER in charge of this application

COMMISSIONER OF PATENTS AND TRADEMARKS

ADVISORY ACTION

THE PERIOD FOR RESPONSE:

a) is extended to run _____ or continues to run _____ from the date of the final rejection
b) expires three months from the date of the final rejection or as of the mailing date of this Advisory Action, whichever is later. In no event however, will the statutory period for the response expire later than six months from the date of the final rejection.

Any extension of time must be obtained by filing a petition under 37 CFR 1.136(a), the proposed response and the appropriate fee. The date on which the response, the petition, and the fee have been filed is the date of the response and also the date for the purposes of determining the period of extension and the corresponding amount of the fee. Any extension fee pursuant to 37 CFR 1.17 will be calculated from the date of the originally set shortened statutory period for response or as set forth in b) above.

Appellant's Brief is due in accordance with 37 CFR 1.192(a).

Applicant's response to the final rejection, filed 3/2/99 has been considered with the following effect, but it is not deemed to place the application in condition for allowance:

1. The proposed amendments to the claim and /or specification will not be entered and the final rejection stands because:
 - a. There is no convincing showing under 37 CFR 1.116(b) why the proposed amendment is necessary and was not earlier presented.
 - b. They raise new issues that would require further consideration and/or search. (See Note).
 - c. They raise the issue of new matter. (See Note).
 - d. They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal.
 - e. They present additional claims without cancelling a corresponding number of finally rejected claims.

NOTE: (no amendment was filed)

2. Newly proposed or amended claims _____ would be allowed if submitted in a separately filed amendment cancelling the non-allowable claims.

3. Upon the filing an appeal, the proposed amendment will be entered will not be entered and the status of the claims will be as follows:

Claims allowed: _____

Claims objected to: _____

Claims rejected: 5, 6, 21 + 24 - 26

However:

Applicant's response has overcome the following rejection(s): _____

4. The affidavit, exhibit or request for reconsideration has been considered but does not overcome the rejection because
see attachment

5. The affidavit or exhibit will not be considered because applicant has not shown good and sufficient reasons why it was not earlier presented.

The proposed drawing correction has has not been approved by the examiner.

Other the sequence Listing submitted 10/30/98 has been entered

PTO Form 892 attached

BEST AVAILABLE COPY

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ATTACHMENT TO ADVISORY ACTION (Paper #21)***Claims Rejections - 35 USC 112***

1. Applicants argue that as evidenced by the articles of Armitage et al. (Eur. J. Immunol, 1992) it is not undue to make a receptor-Ig fusion protein in order to locate a ligand of the receptor. The argument has been fully considered, but is not persuasive. Armitage et al. used the CD40 receptor. One showing in the prior art of an example of successfully identifying the presence and binding of a ligand to a known receptor is not sufficient to show that in the current instance experimentation is undue. Applicants rely on general binding information obtained for mouse 4-1BB as a basis for postulation of binding characteristics of human 4-1BB (e.g., p. 17, lines 20-35, and paragraph bridging pages 11-12). However, looking at properties of the 4-1BB receptors shows that binding properties are complex and not conserved from one species to another. After the effective filing date of the instant application, Loo et al. (X, J. Biol. Chem, 1997) showed that mouse 4-1BB binding characteristics are not predictive of human 4-1BB. It was shown p. 6452, last sentence and Figure 6) that H4-1BB-Ig bound H4-1BBL (L=ligand), but not LN (a second ligand to which mouse 4-1BB specifically binds), "suggesting that the extracellular matrix binding activity of 4-1BB is not conserved in different species". It is further explained that lack of binding conservation between species is not unique, as shown also for CD2 (p. 6455, col. 1). It is concluded (p. 6455, sentence bridging col. 1-2) that "Based on our data, the function of 4-1BB in the regulation of the immune system of humans and mice may be different." Therefore, as set forth in the previous Office action and as discussed above about the lack of predictability about what the human 4-1BB would reasonably be expected to bind to, it is maintained that undue experimentation would be required.

Applicant argue that Miyamura et al. (J. Clin. Invest., 1996) shows making deletion mutations is not undue so that one could delete regions of SEQ ID NO:2 to find out what region of the protein binds to a cell membrane ligand. The argument has been fully considered, but is not persuasive. Making deletion mutants is an invitation to experiment without an idea of what to

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expect. It is not disclosed what regions of H4-1BB extracellular domain (ECD) would be reasonably expected to bind a ligand. This is particularly true in the absence of a ligand to specifically bind to.

Applicant argue that the pharmaceutical composition is enabled for effective treatment of T cell-mediated immune responses because 1) as illustrated by mouse 4-1BB suppressing T cell-dependent immune responses, 2) the data of Linsely et al. (Science, 1992) who showed that B7 bound CD28 and CTLA-4 and a CTLA-4 ECD-Ig fusion suppressed T cell-dependent antibody response, and 3) 4-1BB production is induced during T-cell activation. The argument has been fully considered, but is not persuasive. As stated in the previous Office action, "No experiments are presented, and basis for the effect of blocking 4-1BB is hypothetical and based on the interaction of CD28 to its counter-receptor B7. Applicant's arguments (page 6, second paragraph) are based on the knowledge that 4-1BB is transcribed during T cell activation. Induction of transcription does not necessarily lead to T cell-dependent immune responses. Second, for the reasons of record, there is a lack of enablement of a pharmaceutical because it carries the requirement of being enabled for treatment. The current application does not provide a reasonable expectation that the claimed composition could be used to treat due to the absence of guidance and information presented in the specification and prior art." Additionally, in light of Loo et al. described in the preceding paragraph, data from mouse is not necessarily predictive of human responses.

Oath/Declaration

2. The Declaration filed on March 2, 1999 under 37 CFR 1.131 has been considered but is ineffective to overcome the Schwarz et al. reference.

The evidence submitted is insufficient to establish a conception of the invention prior to the effective date of the Schwarz et al. reference. While conception is the mental part of the inventive act, it must be capable of proof, such as by demonstrative evidence or by a complete

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disclosure to another. Conception is more than a vague idea of how to solve a problem. See *Mergenthaler v. Scudder*, 1897 C.D. 724, 81 O.G. 1417 (D.C. Cir. 1897). The Declaration is insufficient because there is an insufficient showing of conception. Conception in this case would require actual reduction to practice: a showing that the inventor conceived of at least as much as the reference showed. The reference shows the full-length protein and nucleic acid sequences. In *Amgen Inc v. Chugai Pharmaceuticals Co. Ltd.*, 18 USPQ2d, 1016 (CAFC 1991), it was decided that for complex products, such as nucleic acids, conception is not achieved until reduction to practice is accomplished. The court stated that:

A gene is a chemical compound, albeit a complex one, and it is well established in our law that conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it. See *Oka*, 849 F.2d at 583, 7 USPQ2d at 1171. Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it. It is not sufficient to define it solely by its principal biological property, *e.g.*, encoding human erythropoietin, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. We hold that when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, *i.e.*, until after the gene has been isolated.

In the instant situation, Applicant could not envision the detailed constitution (*i.e.* the sequence) of the extracellular domain coding region nor did Applicant have the nucleic acid encoding the extracellular domain (sequenced or not) in hand prior to Schwartz et al.

Exhibit B shows only a portion of the human 4-1BB, absent evidence to the contrary. The reason is that while the amplification primers were complementary to nucleotide sequences in the extracellular domain of mouse 4-1BB, there is no evidence that the primers were positioned to provide amplification of the full extracellular domain of H4-1BB. The primers referred to in the specification (paragraph bridging pages 14-15) amplify a region encoding approximately amino acids 36-58 and 116-128, not the full-length extracellular domain.

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Applicant's assertion that Exhibit C is a Southern blot in the response (p. 4, end of third paragraph) is contrary to the description in the Declaration. In the Declaration, Exhibit C is described as an autoradiogram of hybridizing host cell comprising a vector with the amplified H4-1BB encoding fragment. Still, the H4-1BB cDNA is not the full-length extracellular domain encoding nucleic acid.

Conclusion

3. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire M. Kaufman, whose telephone number is (703) 305-5791. Dr. Kaufman can generally be reached Monday through Friday from 8:00AM to 4:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee, can be reached at (703) 308-2731.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Official papers filed by fax should be directed to (703) 308-4242. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office. Please advise the examiner at the telephone number above before facsimile transmission.

cmk

March 5, 1999



LORRAINE SPECTOR
PRIMARY EXAMINER